No. 95-28

Supreme Court, U.S.
FILED
SEP 11 1995
CLERK

IN THE
# Supreme Court of the United States
OCTOBER TERM, 1995

SCHERING CORPORATION,
*Petitioner,*
v.
FOOD AND DRUG ADMINISTRATION,
*Respondent.*

**On Petition for Writ of Certiorari to the United States Court of Appeals for the Third Circuit**

## PETITIONER'S REPLY BRIEF

ROBERT P. REZNICK
*Counsel of Record*
HUGHES HUBBARD & REED
1300 I Street, N.W.
Suite 900 West
Washington, D.C. 20005
(202) 408-3740
*Counsel for Petitioner*

*Of Counsel*
JOSEPH C. CONNORS
MAUREEN O. CHELIUS
SCHERING CORPORATION
2000 Galloping Hill Road
Kenilworth, NJ 07033
(908) 298-4741

WILSON - EPES PRINTING CO., INC. - 789-0096 - WASHINGTON, D.C. 20001

## RULE 29.1 STATEMENT

Petitioner incorporates by reference the rule 29.1 statement set forth in the Petition for Certiorari at i.

TABLE OF CONTENTS


| | Page |
|---|---|
| RULE 29.1 STATEMENT | i |
| TABLE OF AUTHORITIES | iv |
| ARGUMENT | 1 |
| I. THE THIRD CIRCUIT'S JUDGMENT THAT THE HATCH-WAXMAN AMENDMENTS DO NOT ESTABLISH A JUDICIALLY-ENFORCEABLE STANDARD FOR HEALTH AND SAFETY IN THE APPROVAL OF GENERIC DRUGS BY FDA IS CONTRARY TO THE STATUTE'S PLAIN LANGUAGE, STRUCTURE, AND LEGISLATIVE HISTORY | 2 |
| II. FDA'S CONSTRUCTION OF THE BIOEQUIVALENCE REQUIREMENT IS NOT A PERMISSIBLE ONE | 6 |
| CONCLUSION | 8 |

## TABLE OF AUTHORITIES

*CASE* Page

*Chevron U.S.A., Inc.* v. *Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984) ..... 6, 8

*STATUTES, RULES AND REGULATIONS*

21 U.S.C. § 355(j)(6)(A)(i)(III) ..... 3
21 U.S.C. § 355(j)(7)(A) ..... 2, 3, 4
21 U.S.C. § 355(j)(7)(B) ..... 2, 3
21 C.F.R. § 320.1(e) (1977) ..... 3, 6
21 C.F.R. § 320.22 (1977) ..... 7
21 C.F.R. § 320.23 (1977) ..... 7

*OTHER AUTHORITIES*

Letter dated November 16, 1984 from Harry M. Meyer, Jr., M.D., Director, Center For Drugs and Biologics, FDA, to interested persons.....Appendix

IN THE

# Supreme Court of the United States

OCTOBER TERM, 1995

---

No. 95-28

---

SCHERING CORPORATION,
*Petitioner*,

v.

FOOD AND DRUG ADMINISTRATION,
*Respondent*.

---

**On Petition for Writ of Certiorari to the United States Court of Appeals for the Third Circuit**

---

## PETITIONER'S REPLY BRIEF

---

### ARGUMENT

FDA's Brief in Opposition ("Opp.") confirms that the decision of the court of appeals is as significant as Schering stated in its Petition and that this case is fit for review by this Court. There is now no question as to the potential reach of the court of appeals' holding: FDA is not bound by a congressional standard of safety or efficacy in the approval of any generic drug sold in this country. This holding undoes a critical safeguard of the landmark Hatch-Waxman Amendments. Generic drug approvals continue unabated, and review of FDA's erroneous and self-serving view of that statute should occur without delay.

FDA appeals repeatedly in its Opposition to the deference owed an agency's construction of an ambiguous statute, but this is not a case about deference. Rather,

the question presented is whether FDA should be permitted administratively to reclaim authority specifically taken from it by Congress in 1984—the authority to approve generic drugs even if they are not bioequivalent to the pioneers which they copy. Clearly FDA has no such authority and its assertion of that authority under the guise of purporting to give "bioequivalence" a flexible meaning should have been rejected by the court of appeals. It was not, because that court, following FDA's lead, failed to address substantial affirmative statutory evidence confirming that Congress understood that it was writing into the statute the one, fixed definition that bioequivalence had historically enjoyed. FDA's Opposition glosses over the shortcomings of the court of appeals' decision, and is unresponsive to the overwhelming majority of arguments made in the Petition.

## I. THE THIRD CIRCUIT'S JUDGMENT THAT THE HATCH-WAXMAN AMENDMENTS DO NOT ESTABLISH A JUDICIALLY-ENFORCEABLE STANDARD FOR HEALTH AND SAFETY IN THE APPROVAL OF GENERIC DRUGS BY FDA IS CONTRARY TO THE STATUTE'S PLAIN LANGUAGE, STRUCTURE, AND LEGISLATIVE HISTORY

It does not take long to respond to the only plain language argument that is made in the Opposition. That argument is a simple syllogism: the definition of "Bioavailability" (Section 355(j)(7)(A)) employs the word "means," and is exclusive; the definition of "Bioequivalence" (Section 355(j)(7)(B)) does not, and therefore it must be non-exclusive. Opp. 6. This is not statutory analysis, however, but an exercise in question-begging. The use of "means" certainly connotes an exclusive definition, but the language used by Congress to define bioequivalence *also* connotes an exclusive definition, and indeed has been used to introduce other exclusive definitions in the Food, Drug, and Cosmetic Act ("FDCA"). *See* Pet. 17-18. There is no textual basis for choosing one

definitional formulation over another or, more to the point, for claiming that only one and not both definitions can be exclusive.

FDA's focus on the absence of "means" in the definition of bioequivalence is perhaps the most improbable and insubstantial argument that could be launched, and only highlight's the agency's failure to address—even to *mention*—its own 1977 regulation defining bioequivalence. This regulation was the model for the statute and the predecessor of the regulation presently at issue. Schering and FDA agree that Sections 355(j)(7)(A) and (j)(7)(B) codified "almost verbatim" and "in all pertinent respects" FDA's 1977 regulatory definitions of bioavailability and bioequivalence, respectively, which were in force in 1984. *See* Pet. 19; J.A. 19, 27. Both of those definitions, however—*including the definition of bioequivalence*—employed the word "means," and were understood by FDA to set forth an exclusive, absorption-based definition. *See* Pet. 19; App. 52a. How could an exclusive definition—one that even contains the talismanic word "means"—be codified and yet lose its exclusive character? Neither FDA nor the court of appeals answers this question, or even refers to the regulatory definition (21 C.F.R. § 320.1(e) (App. 52a)) on which the statutory term is based.[1]

So far as statutory structure is concerned, FDA merely endorses without discussion the court of appeals' erroneous conclusion that another provision of the Hatch-Waxman Amendments, 21 U.S.C. § 355(j)(6)(A)(i)(III), "suggests" (J.A. 16a) that bioequivalence need not

---

[1] The disappearance of the word "means" upon the codification of FDA's regulatory definition of bioequivalence is easily understood as an artifact of drafting. The 1977 regulation formally defined "bioequivalent drug products." Congress rephrased it to define when drug products are "bioequivalent," perhaps to be more parallel with the unchanged definition of "bioavailability," and in the process the word "means" became inappropriate and superfluous. *Compare* App. 52a *with* App. 50a.

be based on absorption. That section, however, is not a definitional provision. Rather, it requires FDA to publish a list of every approved drug product and state for each *how* bioequivalence may be shown, either by *in vitro* (test tube) or *in vivo* (in the body) tests. FDA asserted that *in vitro* tests cannot measure absorption, and because Congress recognized that an *in vitro* bioequivalence test might be used, the court of appeals inferred that absorption cannot be essential to bioequivalence. But the premise is flat wrong: *in vitro* tests may indeed show absorption, when they are correlated with *in vivo* tests and therefore are probative of whatever *in vivo* tests may show. Indeed, FDA contemporaneously with passage of the Hatch-Waxman Amendments declared that it would only accept *in vitro* tests that were so correlated.[2] Merely acknowledging that an *in vitro* test may be used to show bioequivalence is thus no evidence that a measurement of absorption is unnecessary.

What the court of appeals did not recognize about the statutory structure, and what FDA ignores entirely in its Opposition, is that the presence of the companion and concededly exclusive definition of bioavailability in Section 355(j)(7)(A) proves that the court's conclusion was wrong. Bioavailability and bioequivalence, both of which had parallel exclusive definitions in FDA's own 1977 regulations, have in addition always been defined *in pari materia*. As FDA itself stated with commendable economy, and as the court of appeals recognized, "bioequivalence is universally understood to mean comparable bioavailability." App. 16a & n.10. In this Court, however, FDA contends that Congress, in the very process of attempting to codify the two provisions unchanged, cleaved them apart by transforming bioequivalence from a definition to a safe harbor. This is no mere matter of

---

[2] *See* letter dated November 16, 1984 from Harry M. Meyer, Jr., M.D., Director, Center for Drugs and Biologics, FDA, to interested persons at Paragraph 7. Pertinent portions of the letter are reproduced in the attached Appendix.

semantics, but what this case is about: the practical difference between an exclusive definition, which limits agency discretion, and a "safe harbor," which is a grant of administrative discretion, is enormous. It has as its endpoint whether FDA may act without the discipline imposed by the threat of effective judicial review. How FDA can argue that Congress' created so fundamental a difference between bioavailability and bioequivalence while attempting to codify their prior meaning "in all pertinent respects" is inexplicable, and FDA does not even try.[3]

While these specific statutory provisions were overlooked in FDA's Opposition, the agency missed the forest as well as the trees. FDA acknowledges (Opp. 10) that Congress added a statutory bioequivalence requirement for the first time in 1984, but to read the Opposition one would conclude this was an irrelevant gesture in what was only a rubber-stamping of FDA's prior practices. Nothing could be further from the truth.

Understanding the statutory bioequivalence requirement is utterly crucial both to the post-Hatch-Waxman generic drug approval process and to the disposition of this case. Congress' imposition of the first mandatory, nonwaivable bioequivalence requirement in 1984 did not extend but fundamentally changed FDA's preexisting practice. Prior to passage of the statute, FDA was free to determine whether or not bioequivalence would be required in connection with a particular generic drug approval.

---

[3] FDA incorrectly attributes to Schering the argument that nonsystemically effective drugs can never be subject to generic competition under an absorption-based bioequivalence standard. Opp. 4 n.3, 5 n.5. Schering makes no such argument. As FDA itself understands, *all* drug products—including NSEDs—are absorbed, J.A. 39, and thus are capable of satisfying the statutory definition of bioequivalence. While measuring the absorption of various products, including many NSEDs, has always presented dfficulties, there is no evidence whatsoever in the record to the effect that it cannot be done now or is not capable of being done in the future.

The agency could determine that the rigorous bioequivalence standard was unnecessary for a given product, in which case it was free to employ whatever lesser standard of similarity to the pioneer product that it deemed appropriate. If, however, FDA required a showing of bioequivalence, 21 C.F.R. § 320.1(e) (1977) set forth the one definition of bioequivalence which applicants had to satisfy. All this changed in 1984. After Hatch-Waxman, FDA had no choice but to require in every instance that a generic be shown bioequivalent to the pioneer it was copying. Pet. 4; attached Appendix ¶ 8.

FDA's pre-1984 authority not to require bioequivalence —to be free instead to vary its approval criteria on a case-by-case basis—is precisely the discretion the court of appeals has allowed FDA to steal back administratively.

## II. FDA'S CONSTRUCTION OF THE BIOEQUIVALENCE REQUIREMENT IS NOT A PERMISSIBLE ONE

FDA, again with little more than citation to the court of appeals' decision, argues under the second prong of the *Chevron* test that Congress specifically intended to codify the agency's allegedly historical discretion to give bioequivalence whatever meaning it wished on a "case-by-case" basis, and that FDA's regulation thus must be reasonable. Opp. 10-11. FDA, however, does not and cannot support its erroneous characterization of either Congress' actions or its own.

First, FDA's reliance upon general statements that Congress intended to extend the then-existing generic drug approval process have no force as to the question presented in this case. As explained above, while the Hatch-Waxman Amendments codified certain of FDA's prior terms and procedures, it changed the law fundamentally by adding the bioequivalence requirement. Those changes, ignored by FDA and the court of appeals, are what this case is about.

Second, FDA's claim to have historically given bioequivalence a flexible meaning (Opp. 11) is undocumented, unattributed, and simply wrong. Of all the possible questions involving the generic drug approval process, none could be less subject to debate than FDA's understanding of the meaning of bioequivalence prior to 1984. That definition was established by a published regulation and was written in what FDA itself acknowledges were exclusive terms that required a showing of absorption. *See* Pet. 18-19; App. 52a. Neither FDA nor the court of appeals cites any evidence whatsoever to support the improbable claim that the regulatory definition was ignored.[4]

It also remains the case that FDA's construction is unreasonable because the agency has become too willing to sacrifice the statutory safety requirement in its pursuit of generic drug approvals. Quoting the court of appeals, FDA says to this Court that bioequivalence occurs "when two drugs possess the same efficacy." Opp. 2. Perhaps omitting the requirement of comparable *safety* from the drug approval process was a slip of the pen; mistake or not, the error is now part of the case law and will remain so unless the Petition is granted. In any event, that misstatement of the law is precisely the one that the court

---

[4] FDA asserts in a footnote that FDA's 1977 bioequivalence regulations apply to both systematically effective and nonsystemically effective (topical) drugs, and that regulatory provisions in effect in 1984 "provided for bioequivalence to be established by means other than actual measurement of rate and extent of absorption." Opp. 7 n.7. Schering agrees that the 1977 regulations applied to all drugs, as do the ANDA provisions of the FDCA today. As to the regulations cited, it is enough to say that two (21 C.F.R. §§ 320.22 and .23 (1977)) refer to *bioavailability*. Bioavailability, then as now, can only be defined in terms of absorption (*see* Opp. 6, 10); FDA's claim that the regulations prove that measurement of absorption is unnecessary is thus quite obviously wrong. The remaining two provisions merely list permissible test methodologies to satisfy the contemporaneously adopted regulation defining bioequivalence exclusively in terms of absorption.

of appeals told FDA it had made elsewhere in arguing that the goal of the Hatch-Waxman Amendments to encourage generic competition took precedence over health and safety concerns. *See* Pet. 25-26, App. 12a-13a. FDA is wrong about the statute, and the court of appeals was wrong under the banner of *Chevron* to have written the error into law based upon a misguided notion of deference.

## CONCLUSION

The Petition For Certiorari should be granted.

Respectfully submitted,

ROBERT P. REZNICK
*Counsel of Record*
HUGHES HUBBARD & REED
1300 I Street, N.W.
Suite 900 West
Washington, D.C. 20005
(202) 408-3740
*Counsel for Petitioner*

*Of Counsel*
JOSEPH C. CONNORS
MAUREEN O. CHELIUS
SCHERING CORPORATION
2000 Galloping Hill Road
Kenilworth, NJ 07033
(908) 298-4741